-- 14 ~~16~~. A method for providing local anesthesia or analgesia to a mammal which comprises topically applying to said mammal a composition containing phospholipid vesicles encapsulating 0.1 to 10% by wt. of an anesthetic or analgesic agent, wherein said composition is applied in an amount between about 0.005 to 0.5 g/cm^2 of surface to be anesthesized. --

REMARKS

Claim 1 has been amended in a manner indicated by the Examiner to place it in form for allowance. In particular, the recitations of claims 3, 4 and 12 have been added and claims 3 and 4 cancelled. Also, new claim 16 has been added. No new matter has been added to the application. Claims 1, 2, and 5-16 are now pending.

The subject invention is directed to a method for providing local anesthetic and analgesic treatment for human and veterinarian purposes. The inventive method involves topically applying local anesthetics and analgesics encapsulated within lipid vesicles, particularly phospholipid vesicles. It has been shown, see particularly Tables 1-4 of the application, that the topical application of liposomes containing local anesthetics and analgesics enhances the penetration and localization of the anesthetic and analgesic agents relative to conventional topical preparations such as ointments and creams.

Claims 1, 2, 5-11 and 16 are directed to the method for providing local anesthesia and analgesia, whereas claims 12-15 are directed to a pharmaceutical composition containing lipid vesicles with specifically enumerated local anesthetic agents and analgesic agents encapsulated therein.

Claims 1-15 are rejected under 35 USC §103 as being unpatentable over Janoff U.S. 4,721,612 in view of Haynes U.S. 4,725,442. This rejection is respectfully traversed.

Janoff '612 pertains to the preparation of liposomes (lipid vesicles) by employing a salt form of an organic acid derivative of a sterol, such as the tris-salt form of a sterol hemisuccinate. The modified-sterol liposomes are particularly useful for administering entrapped compounds in vivo. Janoff, at Col. 10, lines 50-65, provides a shotgun disclosure of 31 different classes of biologically active compounds that can be entrapped using his modified-sterol liposomes. Local anesthetics are one of the enumerated classes. Janoff also discloses the full gambit of administration routes at Col. 10, lines 66 to Col. 11, line 7, including the use of topical application. Janoff does not, however, specifically suggest or disclose using topical application of liposomes containing a local anesthetic for the purpose of providing a local anesthetic effect, and particularly does not recognize that enhanced penetration and localization is obtained with this method of administration.

The one example that Janoff does present using an analgesic-type drug effectively teaches away from the present invention. In Example 10.1, Janoff describes treating joint arthritis with liposomes containing indomethacin, an analgesic agent. Instead of applying the composition topically, however, Janoff employed the intramuscular injection of the indomethacin-containing lipid vesicles. Like Example 10.1, all of the other Examples in Janoff also are directed to the use of injection as the mode of administering the liposomes containing the biologically active or pharmaceutical compounds. Janoff does not present a single example using his liposomes for topical application of a drug.

Even if Janoff '612 makes it prima facie obvious to topically apply liposomes containing an anesthetic or analgesic agent, a point which applicant seriously doubts, applicants' surprisingly unexpected showing in the patent application that enhanced penetration and localization is obtained by this method of treatment, particularly when using liposomes made with phospholipids (claim 16), effectively rebuts such a prima facie case.

In Example 10.3, Janoff presents evidence showing that his particular liposomes are different from liposomes made using conventional phospholipids in the way that they are distributed **in vivo**. Thus, there is a suggestion that his liposomes behave differently from those made using conventional ingredients and procedures. Claims 7-11 and 16 of the subject application are directed specifically to liposomes made from conventional phospholipids. Janoff does not render obvious a method for providing local anesthesia using phospholipid vesicles containing anesthetic agents.

Haynes '442 specifically relates to a method for obtaining local anesthesia by intradermal or intravenous **injection** of general anesthetics, and broadly pertains to the injection of other water-insoluble anesthetics or drugs using microdroplets smaller than one micron having a phospholipid monolayer. Haynes' microdroplets are not liposomes. Thus, Haynes does not disclose incorporating local anesthetics such as benzocaine into a liposome.

If anything, Haynes underscores Janoff's lack of a specific teaching to administer local anesthetics **topically** using liposomes. Surely, Haynes, which is devoted specifically to the injection of general and local anesthetics would not make it obvious to depart from that administration procedure when employing Janoff's liposomes,

particularly where Janoff in all his Examples, including one of an analgesic-type drug, also employs injection techniques.

Janoff's teaching that his sterol-derived liposomes differ from conventional phospholipids and his failure to disclose or suggest topical application for local anesthesia, coupled with applicants' surprising discovery that topical application of such local anesthetics and analgesic agents, particularly those identified in claims 3, 10 and 12, entitles applicants to a patent for their discovery.

Reconsideration of the pending application is respectfully requested.

Respectfully submitted,

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January 16, 1990